Chemistry and Toxicology Devices
April 25, 2013

Phencyclidine (PCP) Test Systems

Executive Summary

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PCP Test Systems

Executive Summary

I. *Introduction*

The purpose of this meeting is to determine the appropriate regulatory classification for diagnostic devices known as Phencyclidine (PCP) Test Systems. PCP Test Systems are considered pre-amendment devices since they were in commercial distribution prior to May 28, 1976 when the Medical Device Amendments became effective, but have not yet been classified. The Food and Drug Administration (Agency) is seeking panel input on the safety and effectiveness of Phencyclidine (PCP) Test Systems in order to classify these devices.

II. *Regulatory History*

The Agency classifies medical devices into Class I, II, or III generally determined by the risks or hazards to the patient or user associated with the device. Class I devices are those devices which are considered low risk and present minimal potential harm to a user. The risks from harm of a Class I device can be adequately mitigated by general controls which include the following:

- Establishment registration and listing;
- 510(k) premarket notification;
- Good Manufacturing Practices (GMPs); and
- Other regulatory controls, e.g., labeling adverse event reporting, misbranding, adulteration of the device, and others.

Subsequently, many of the Class I devices have been exempted from the 510(k) premarket notification procedures due to their low risk. However, they have not been exempted from other general controls.

Class II devices are those devices which are considered to have moderate risk such that general controls alone are not sufficient to mitigate the risks of harm to a user and for which there is sufficient information to establish special controls, existing methods specific to the device that can control the risks not controlled by the general controls. Special controls for medical devices may include:

- Performance standards;

- Post-market surveillance;
- Patient registries;
- Design controls; and
- Other appropriate actions deemed necessary for mitigating the risks of the device.

Class III devices are those devices considered to be high risk and whose risk may not be completely mitigated by general and special controls alone. For Class III devices there is insufficient information to establish a reasonable assurance of safety and effectiveness so data from a well-controlled, statistically significant clinical study is often needed. These devices are typically life sustaining or life supporting, of substantial importance in preventing impairment of human health, or present an unreasonable risk of illness or injury.

After the Medical Device Amendments of 1976 were enacted, recommendations for the classification of existing medical devices by their risks into Class I, II, or III were obtained in a series of classification panel meetings. During that process, tests for common drugs of abuse such as amphetamines, cannabinoid, cocaine, opiates, methamphetamine, benzodiazepines, and others were classified as Class II devices requiring premarket notification and clearance prior to marketing. However, PCP Test Systems were not included in the original device classification process and were therefore not assigned a device classification. For the last 37 years, PCP tests have been reviewed by the Agency through the premarket notification [510(k)] process but have remained unclassified. More than 200 PCP tests have been cleared in that time[1].

III. *Indications for Use*

The indications for use in general, is a description of the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.

PCP tests are generally designed to detect the presence of PCP in blood, urine, sweat, saliva, hair, or other matrices. These devices may be indicated for initial testing (screening) or confirmation of presumptive positive samples. PCP tests may be for:

- Prescription use - in a central clinical chemistry laboratory,
- Point of Care Use – prescription use at doctor's office labs, in the emergency department or at the patient bedside,
- Over-the-Counter (OTC) use, or
- Workplace use – may be prescription or OTC.

[1] For a list of FDA cleared PCP Test Systems, follow the link to the FDA 510(k) database: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
Search under product codes: LCM (PCP, enzyme immunoassay), LCL (PCP, radioimmunoassay), and LCK (thin layer chromatography).

IV. *General Device Description*

PCP test system methodology is varied. For example, PCP test systems include high-throughput screening tests run on clinical chemistry immunoassay analyzers, point-of-care lateral flow chromatographic immunoassays, and highly complex and specific methods such as liquid chromatography tandem mass spectrometry (LC-MS/MS).

The following are examples of the varied settings in which PCP testing is performed and interpreted.

Laboratory/clinical settings: (e.g. hospital lab, physician office lab, emergency department)

- Trained laboratory workers, health care professionals without laboratory backgrounds, and/or trained lay users perform drugs of abuse screening using instrument systems or single-use devices
- A physician ordinarily reviews preliminary and confirmatory results and considers other information about the patient when drawing conclusions

Home settings:

- Untrained users that are not expected to be proficient in testing perform drugs of abuse screening tests with single-use devices
- Home users may or may not understand the meaning of false positive and false negative results
- All FDA cleared home use devices include a mailer for the user to send the positive specimen for confirmatory testing

Workplace, sports, and insurance settings:

- Testing is often performed repetitively
- The risk of getting an inaccurate or unreliable result will vary depending on factors such as the setting, the training of testing personnel, the volume of use, and access to trained medical review officers (MROs)
- Where MROs are available, decisions about the accuracy and reliability of any given result can be made in the context of additional medical information about the testing subjects
- Phencyclidine is among the five drugs required by the Department of Health and Human Services (DHHS) to be tested in the federal workplace

Drug tests, including PCP tests, are typically qualitative tests that report results as positive or negative relative to a designated threshold or cutoff. The cutoff concentration for PCP (25 ng/mL) in urine is set by the Department of Health and Human Services (DHHS) to define a positive result for workplace drug screening, [1,2] and most other screening programs (including clinical point-of-care testing) adopt the same cutoff for screening. PCP cutoff concentrations for other matrices and for other purposes have been suggested in the literature, but all laboratories/programs should evaluate cutoff values for their specific patient population. Cutoffs are generally set at the point at which a drug is not only detectable, but can be differentiated precisely from other, possibly endogenous, interfering substances in the sample. [3] If the

concentration of drug in the sample is above the cutoff value, the sample is regarded as positive, and if it is below the cutoff value, it is considered negative.

V. *Current FDA Establishment Registration and Device Listing*

There are currently many manufacturers who list PCP test systems in the Agency's registration and listing database. For a complete list you may search the registration and listing database. Follow the link (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm), select "Registration and Listing" (under Other Databases), and search for product codes LCM, LCL, and LCK.

VI. *Risks and Mitigations of PCP Test Systems*

For the purposes of classification, the FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended:
2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. The reliability of the device.

Part (g)(1) of this regulation further states that it "is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into class III."

Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the devices for its intended uses and conditions of use."

Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e) (1), "[t]here is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

Phencyclidine History and Use

PCP (also referred to as "angel dust") was initially synthesized in the 1950s as an anesthetic, but it was quickly removed from the market due to unpredictable behavioral reactions that occurred during recovery from anesthesia. The drug is highly lipophilic and can be administered by oral and intravenous routes, as well as by smoking. It is usually abused due to its euphoric and hallucinogenic effects. Today, detection of PCP use in the United States is rare because the drug is no longer widely abused.[4]

The psychedelic effects are seen for approximately one hour after ingestion. The detection time after smoking PCP is 5 to 15 minutes in the serum and approximately 8 days in the urine. Blood concentrations ranging from 20 to 30 ng/mL can produce excitation and seizures, and death can occur at levels above 100 ng/mL. The majority of PCP is hydroxylated and then glucuronidated; the metabolites are excreted renally. Up to 15% is eliminated unchanged in urine.[5]The elimination half –life is usually about 3 days, but urinary acidification can increase the speed of elimination and decrease the half-life to 1 day.[6] Though typically PCP can be detected in urine for about 1 week, this may increase to 2-4 weeks in long-term users.

Drugs of Abuse Testing

Screening tests generally are performed to identify presumptively positive specimens. Positive screening results are followed by confirmation with a different, a more specific analytical test, usually gas chromatography/mass spectrometry (GC/MS). Confirmation utilizing a more specific method is necessary since immunoassays, which are widely used as screening tests, have a relatively high rate of false positive (FP) and false negative (FN) results. FP results are generally due to the fact that the antibodies used in immunoassay technologies may recognize substances which may have similar structural features as the drug of interest. Confirmation testing is generally much more accurate, and can distinguish between drugs, their metabolites, and other interfering substances in the sample. Confirmation testing of screen positive results is performed by laboratories that use more specific alternative chemical methods such as GC/MS or LC-MS/MS. In addition, clinical consideration and professional judgment should be applied to any drug-of-abuse test result.

In the United States, medical testing and most drug screening programs require confirmation of all positive screening test results and all invalid tests or runs. This enables good statistics of the false positive rates for PCP and other drug tests. The Substance Abuse and Mental Health Services Administration (SAMHSA) reports that 50% of PCP screening tests are false positive tests (i.e., tests that do not confirm as positive tests with follow-up confirmation testing). High quality testing programs will generally also perform confirmation testing on a portion of negative tests. However, because in most populations, the number of negative screening results far

exceeds the number of positive results, even if 10% of the negative results are confirmed, it is difficult to get a good estimate of the false negative rate for any particular program. There is little information on the rate at which OTC test results, even positive results, are confirmed.

Various body fluids and tissues can be tested for the presence of drugs, such as blood, saliva, hair, sweat and urine. Each sample matrix has advantages and disadvantages. For example, urine testing, which is frequently used, is noninvasive and contains relatively high concentrations of drugs and their metabolites for a reasonable duration after ingestion.[7] However, the concentration of drugs and drug metabolites in urine are influenced by urine flow, pH, hydration status, and metabolism. Urine commonly indicates the presence or absence of drugs, but it cannot easily be used to quantify levels or to determine the time or duration of use. Thus it is not generally possible to prove whether an individual abuses a drug habitually, or sporadically and casually. Also, it is not possible to correlate the presence of an abused substance in the urine with any specific degree of central nervous impairment in the user. Saliva samples are easily obtainable for testing and avoid the privacy and collection issues inherent to urine testing, but drugs can only be detected in saliva for hours to days rather than days to weeks for urine samples. Therefore, it is important that test matrices are chosen carefully for each particular testing purpose.

Risks to Health

For *in vitro* diagnostic devices, the majority of the risks to health are not direct risks of device use (e.g., needle sticks, burns, etc.) but are indirect risks. That is, the risk is generally related to the impact of the decisions made in treatment of a patient based on an undetected FP or FN test result. For example, the use of a drugs of abuse test in the emergency department does not introduce much risk through the collection of urine and use of the test device. However, if a FP drug test is used to triage a patient that has a more serious condition (e.g., stroke), there is potentially a risk to the patient due to delay in treatment for the correct condition.

False Positive Results

The impact of a FP PCP test result will vary by the type of test and the setting of use. For example, in formalized drug screening programs, false positive screening tests are all confirmed by a more accurate test method, so there is little risk of incorrect actions based on that result alone. In situations where confirmation is not performed (e.g., an OTC user may not understand the need for confirmation), or is delayed (e.g., an emergency department may act on a screening test result if it fits the clinical picture while awaiting confirmation), there may be more risk. FP confirmation tests will have some consequence, and that consequence will vary based on the reason for testing.

FP results are most commonly due to cross-reactivity of the assay with substances that have structural similarity to PCP. Many agents are described as eliciting PCP FP results. Diphenhyramine, ketamine, lamotrigine, thioriadizine, venlafaxine, tramadol, ibuprofen, imipramine, meperdine, mesoridizine and o-desmethylvenlafaxine have been identified in clinical studies to be able to cause FP PCP results when tested by qualitative immunoassay drug

screens.[4,8-13] The systems are based on antibody binding to the drug, so that chemically related compounds or metabolites commonly cross-react, causing a FP result.

One reviewed publication, *Using molecular similarity to highlight the challenges of routine immunoassay-based drug of abuse/toxicology screening in emergency medicine* , provided information as to the frequency of interference caused by molecularly similar prescription drugs resulting in FP PCP results. [14] The article noted that although the use of PCP as a drug of abuse has waned significantly over the past twenty years, there are still a greater than expected number of positive PCP results from drug screens which are later confirmed to be FPs. The author attributes the FP results to the increase in use of certain prescription drugs which are molecularly similar to PCP. For example venlafaxine is the 55th most prescribed drug in 2008 and dextromethorphan continues to be widely used as both a prescription and over-the -counter medication in anti-tussive remedies. Within 24 months, the author's emergency department had ten positive PCP drug screen results. Upon confirmation with GC-MS, only one of these samples contained definitive amounts of PCP.

Other potential causes of FP results may include, for example, imprecision, bias, test design flaws (e.g., ineffective antibodies), device malfunctions, calibration errors or drifts, contaminated or expired reagents, and pre-analytical errors (e.g., incorrect specimen collection and/or storage).

False Negative Results

The impact of a FN PCP test result will also vary by the type of test and the setting of use. For example, FN screening tests are typically not confirmed by a more accurate test method, so the patient will be presumed to be negative for the presence of PCP. FN PCP confirmation tests are generally considered accurate, and will generally be accepted as valid in the absence of evidence of device malfunction. The consequence will vary based on the reason for testing. For example, in some cases, the additional, unnecessary testing may be performed while in other cases, individuals may be allowed to perform high risks task that may endanger themselves or others (e.g., pilots, construction workers).

Potential causes of a FN PCP result may include, for example, imprecision, bias, test design flaws (e.g., ineffective antibodies), device malfunctions, calibration errors or drifts, contaminated or expired reagents, and pre-analytical errors (e.g., absorbance of drug to collection device material).

The following sections describe how the pre- and postmarket regulation may help to mitigate the risks associated with PCP test systems.

VII. *Agency Review of In Vitro Diagnostic Devices*

As described above, FDA regulation of medical devices is meant to help mitigate the potential risks of those devices. For example, general controls such as the requirement for Good Manufacturing Practices provides assurance that devices are designed under a Quality System and that device remains safe and effective when manufactured over time (e.g., maintain lot-to-lot

consistency). Similarly, premarket review provides assurance that the characteristics of the device (including analytical and clinical performance) are appropriate for its intended use and that the labeling provides adequate instructions for use (including appropriate precautions, where necessary).

Special controls, often implemented for class II devices, provide even greater assurance that devices are as safe and effective as other similar devices. For example, a performance standard special control would assure that all devices meet a certain minimum standard necessary for safe use of that device. Though performance data and labeling claims for Class II *in vitro* diagnostic devices are generally reviewed by the Agency prior to marketing, manufacturers do have some flexibility in modifying these types of devices and their labeling once the devices are on the market without further FDA review.

Premarket approval provides the highest level of assurance that a device is safe and effective and remains safe and effective over time. Once a device is approved, manufactures cannot make any changes to the Class III device or to the device labeling without notifying and receiving approval from FDA. (Refer to Appendix A for examples of Class I, II and III in vitro diagnostic devices)

As discussed above, though all other drugs of abuse tests were classified as class II and require 510(k) clearance prior to marketing, PCP was never classified. Since the Agency never called for PMAs, PCP tests have been cleared through the 510(k) process for nearly 4 decades. The Agency has cleared hundreds of PCP test systems in that time period; however, there are occasionally PCP submissions that are reviewed but not cleared for marketing, primarily because of performance deficiencies.

Agency review of *in vitro* diagnostic devices assesses the following characteristics (where applicable) of an assay submitted for clearance:

- Indications for use
- Special Conditions for use
- Instrument requirements
- Device Description
- Substantial Equivalence information
- Standard/Guidance Documents Referenced
- Test principle
- Performance Characteristics:
    - Precision/reproducibility
    - Linearity/assay reportable range
    - Recovery
    - Traceability
    - Stability
    - Expected values
    - Detection limits (Limit of Blank , Limit of Detection, Limit of Quantitation)
    - Specificity/Cross reactivity/Interferences
- Method Comparison/Accuracy
- Matrix comparison
- Labeling

- Software

As stated above, examples of potential causes of FP and FN PCP results include interferences, imprecision, bias, test design flaws, device malfunctions, calibration errors or drifts, contaminated or expired reagents, and pre-analytical errors. 510(k) review of PCP devices can address many of these issues, including interferences, imprecision, bias, test design flaws, and pre-analytical errors. In addition, as part of the review the Agency ensures that the labeling clearly communicates the information necessary for safe use of the device.

VIII. *Post-market surveillance, Medical Device Report Query*

The medical device industry and healthcare facilities submit mandatory medical device reports to FDA to help monitor the safety of medical devices. In addition, the Agency receives and reviews voluntary reports from the public. Medical device reports may include deaths, serious injuries, and product malfunctions. This information is used by FDA to learn about post-market performance of a device as well as to identify those devices that are not safe and effective for their intended use. Event reports are analyzed by healthcare clinicians, engineers, and scientists. Follow up actions include additional investigation, requesting information from the device manufacturer, conducting a manufacturer facility inspection, issuing a public health advisory/safety alert, or other enforcement actions. Postmarket regulation helps to mitigate the risk of FP and FN PCP results due to device malfunctions, calibration errors or drifts, and contaminated or expired reagents.

The safety and effectiveness of PCP test systems was further investigated by querying the FDA Medical Device Reports (MDR) database for any adverse reports that may have occurred since PCP test systems have been regulated. Two MDR reports have been submitted for PCP test systems. One report was from 2011 and the other was from 2012. One involved a false positive PCP screening test result. The patient expired before a confirmation with GC-MS could be made. The confirmatory test later proved to be negative for PCP and positive for a drug overdose of methylenedioxypyrovalerone (MDVP). The second MDR report involved seven false positive PCP results which were questioned by the physician. The samples were run by an alternative manual method and the results were found to be negative. The discordant results were caused by incorrect calibration of the analyzer. No patient intervention or adverse health consequences resulted from the discordant results. The Agency has received other MDR reports for other drugs of abuse tests, including reports of FP results in the emergency department leading to delayed treatment of patients. However, the frequency of injury reports for drug tests is relatively low.

IX. *Safety and Effectiveness Summary*

The use of PCP test systems is well established and similar to the use of other tests for abused drugs. FDA premarket review and post-market surveillance of these devices has adequately assured the safety and effectiveness of these tests when used as intended. The Agency believes that the information presented in this Executive Summary, as well as nearly 4 decades of experience in regulation of these devices, suggests that general controls and special controls,

(such as performance standards) would be sufficient to support a reasonable assurance of safety and effectiveness, and would support a class II determination for PCP Test Systems.

X. *Chemistry and Toxicology Devices Advisory Panel Discussion Questions for PCP Test Systems*

Panel Discussion Questions

1. The Agency has provided a summary of some key risks to health due to potential false positive and false negative PCP test results. Using your own knowledge and expertise, please identify any additional risk(s) to health you feel may have been omitted with regards to PCP test systems and how they may be addressed and mitigated (e.g., labeling, additional studies, etc.).

2. Which classification, class I (general controls), class II (special controls), or class III (premarket approval), is most appropriate for PCP test systems?

    a. If Class I is recommended, please explain why you believe that there is sufficient information to determine that general controls alone are sufficient to provide reasonable assurance of safety and effectiveness of PCP test systems. Should premarket notification be one of the general controls required for PCP tests?

    b. If Class II is recommended, please explain why you believe that there is sufficient information to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness of PCP test systems? What special controls would you recommend (e.g., performance standards, labeling, etc.)?

    c. If you believe the device should be classified into class III and made subject to Premarket Approval (PMA), discuss the important clinical and analytical study design features necessary to demonstrate that the device is safe and effective.

XI. *Appendices*

Appendix A
Classification Table

	Class I*	Class II	Class III
Risk	▪ Considered **low risk** ▪ Present minimal potential harm to a user. ▪ Devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness of such devices.	▪ Considered **Moderate risk** ▪ General controls alone are not sufficient to mitigate the risks of harm to a user. ▪ There is sufficient information to establish special controls, existing methods specific to the device that can control the risks not controlled by the general controls.	▪ Considered **high risk** ▪ Risk may not be completely mitigated by general and special controls alone ▪ There is insufficient information to establish a reasonable assurance of safety and effectiveness. ▪ Typically life sustaining or life supporting. ▪ Of substantial importance in preventing impairment of human health, or present an unreasonable risk of illness or injury.
Controls	**General Controls:** ▪ Establishment registration and listing; ▪ 510(k) premarket notification*; ▪ Good Manufacturing Practices (GMPs); and ▪ Other regulatory controls, e.g., adverse event reporting	**General Controls** **Plus** **Special Controls, which may include:** ▪ Performance standards; ▪ Post-market surveillance; ▪ Patient registries; ▪ Design controls; and ▪ Other appropriate actions deemed necessary for mitigating the risks of the device	**General Controls and Special Controls** **Plus** **Premarket Approval:** ▪ Data from a well-controlled, statistically significant clinical study (valid scientific evidence) ▪ Manufacturers cannot make any changes to the Class III device or to the labeling without notifying and receiving approval from FDA.
Examples	▪ Estradiol test system (21 CFR 862.1260) ▪ Follicle-stimulating hormone test system (21 CFR. 862.1300) ▪ Luteinizing hormone test system (21 CFR 862.1485)	▪ Sirolimus test system (21 CFR 862.3840) ▪ Cyclosporine test system (21 CFR 862.1235) ▪ Cocaine and cocaine metabolite test system (21 CFR 862.3250)	▪ Human Papillomavirus (HPV) tests ▪ Non-invasive glucose sensing devices for diabetes ▪ Her2/neu tests for predicting response to Herceptin therapy

*Many of the Class I devices are exempt from 510(k) notification due to low risk

Appendix B
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Appendix C

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Concurrence Page

Chemistry and Toxicology Devices

Phencyclidine (PCP) Test Systems

Classification Executive Summary

Digital Signature Concurrence Table	
Reviewer Sign-Off	Tracey L. Bosworth 2013.03.26 13:59:56 -04'00'
Division Sign-Off	Courtney H. Lias, Ph.D. 2013.03.26 16:11:38 -04'00'